Quantitative Trait Loci Affecting Health Traits in Swedish Dairy Cattle

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ABSTRACT

The purpose of this study was to map quantitative trait loci (QTL) affecting health traits in Swedish dairy cattle. A genome scan covering 17 chromosomes was performed. Ten grandsire families were used in a grand-daughter design. Nine of the families belonged to the Swedish Red and White breed, which is related to other Nordic Ayrshire breeds, and one family was of the Swedish Holstein breed. A total of 417 bulls were genotyped for 116 microsatellite markers distributed over 17 chromosomes. Daughter yield deviations for clinical mastitis, somatic cell count (SCC), and other diseases (OD) were included in the analysis. Least squares interval mapping using putative QTL as cofactors was applied both within and across grandsire families. Significance thresholds were set by permutation tests. In the across-family analysis, we detected 8 suggestive QTL and 3 QTL significant at the genome level. The QTL affecting clinical mastitis were found on 3 chromosomes (9, 11, and 25), 4 QTL for SCC were found (on chromosomes 5, 9, 11, and 23), and we detected 4 QTL for OD (on chromosomes 9, 11, 15, and 25). In addition, we found several QTL that segregated within single families but where the QTL effect was not significant in the across-family analysis. In conclusion, we were able to locate QTL for all 3 analyzed traits, and overlapping QTL for several traits were observed.

(Key words: quantitative trait loci, clinical mastitis, health trait, dairy cattle)

Abbreviation key: BTA = *Bos taurus* autosome, DYD = daughter yield deviation, OD = other diseases.

INTRODUCTION

Health problems in dairy cattle cause considerable economic losses for the producers, including costs of reduced milk production, increased involuntary culling rates, and costs for veterinary treatments. In addition to being an economic problem, diseases also affect the

animal well being, an issue on which there is an increasing focus in many countries today. The most important health problem in dairy cattle is mastitis. Unfavorable genetic correlations between milk production and both mastitis and SCC have been reported in several studies (Emanuelson et al., 1988; Pösö and Mäntysaari, 1996; Rupp and Boichard, 1999). In a review based on data from the Nordic countries by Heringstad et al. (2000), the estimates of the genetic correlation between mastitis susceptibility and milk yield ranged from 0.24 to 0.55 with a mean of 0.43. Thus, udder health must be included in the breeding goal to decrease the incidence of mastitis in the dairy cattle population.

Resistance to mastitis and other health traits is of a complex nature, influenced by many genes and, to a great extent, by environmental factors. The underlying genes or chromosome segments affecting such complex traits have been termed QTL. By using traditional methods of selection, it has been difficult to improve health traits such as resistance to mastitis and other diseases (OD) because of their low heritability. These traits are sometimes difficult to measure properly and, consequently, require an extensive recording to enable an accurate genetic evaluation. If we can identify QTL responsible for a significant proportion of the genetic variation in these low heritability traits or detect closely linked markers that are co-inherited with the QTL, then the genetic progress could be enhanced by using marker-assisted selection.

Most QTL studies reported have been restricted to production traits such as milk yield and composition (Bovenhuis and Schrooten, 2002). The studies concerning udder health have often described QTL for SCC or udder conformation (Heyen et al., 1999; Schrooten et al., 2000; Kuhn et al., 2003), whereas only a few studies deal with QTL for clinical mastitis and OD (Elo et al., 1999; Klungland et al., 2001; Schulman et al., 2002). The latter studies were all done in the Nordic countries, where national disease recording systems have been developed and genetic evaluation for health traits in dairy cattle has been applied during the last 20 yr. These systems provide means to search for QTL directly affecting clinical mastitis and OD in the commercial dairy cattle population.

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Resistance to clinical mastitis and SCC are both expressions of udder health, and the genetic correlation between the traits is moderate to high (Emanuelson et al., 1988; Philipsson et al., 1995; Pösö and Mäntysaari, 1996). However, as the correlation is less than one, SCC and clinical mastitis cannot be considered as expressions of the same trait. One concern over using SCC without including records of clinical mastitis in selection programs is that the selection would not only act to reduce the incidence of clinical mastitis but also would negatively influence the possibility for a cow to respond to an infection. Schukken et al. (1999) showed that SCC was higher prior to *Staphylococcus aureus* challenge in cows that resisted infection than in cows that became infected. However, the nature of the genetic relationship between SCC and clinical mastitis is still under debate. In contrast to the findings of Schukken et al. (1999), other studies (Rogers et al., 1998; Nash et al., 2000) have found a quadratic relationship where daughters of sires that transmit the lowest SCC had the most favorable records of clinical mastitis. Philipsson et al. (1995) found a linear relationship between SCC and clinical mastitis, and they also showed that selection based on both SCC and clinical mastitis was the most efficient strategy in reducing cases of clinical mastitis. To improve the genetic resistance of cows to udder pathogens by use of genetic markers, it is thus important to also consider QTL with an effect on clinical mastitis and not only focus on QTL with large effects on SCC.

The aim of the present study was to locate QTL affecting health traits in the Swedish dairy cattle population. In a partial genome scan over 17 chromosomes using microsatellite markers and a granddaughter design including 10 sire families, we were able to identify regions with QTL for clinical mastitis, SCC, and OD.

MATERIALS AND METHODS

Animals

Animals from the 10 largest dairy cattle half-sib families in Sweden were used in a granddaughter design (Weller et al., 1990). Nine of the families belonged to the Swedish Red and White breed, which is closely related to other Nordic Ayrshire cattle breeds, and one family was of the Swedish Holstein breed. The grandsires were born from 1972 to 1981. The average number of sons per family was 42, ranging from 21 to 58, and the total number of sons genotyped was 417.

Marker Data

The DNA from each bull and grandsire was extracted from frozen semen samples; and genotypes for 116 markers distributed over 17 chromosomes were determined.

Table 1. Linkage groups used in the QTL analysis for health traits in 10 grandsire families of Swedish dairy cattle.¹ Number of informative markers within each sire family, averaged across families, is given per chromosome.

BTA ²	First and last marker of linkage group	Total markers	Average informative markers
			(no.)
1	TGLA49 – URB014	8	5.1
2	TGLA44 – FCB11	7	5.3
3	INRA006 – BM2924	11	6.1
4	BMS827 – MGTG4B	12	7.3
5	BM6026 – BM2830	7	4.6
6	ILSTS93 – BM2320	6	3.8
9	INRA136 – BMS1967	7	4.3
11	BM9067 – HEL13	7	4.8
13	TGLA23 – AGLA232	6	3.7
14	BMS1747 – BM6425	6	4.4
15	BR3510 – RM004	5	3.1
18	BMS1355 – TGLA227	7	5.4
19	HEL10 – BMC1013	7	4.3
22	CSSM026 – BM4102	6	4.7
23	CSSM5 – BM1443	6	4.1
25	ILSTS102 – BMS1353	4	2.5
29	BMS1244 – ILSTS81	4	2.9
Total		116	76.4
Average		6.8	4.5

¹Nine families of the Swedish Ayrshire breed and one of the Swedish Holstein family.

²BTA = *Bos taurus* autosome.

Number of markers per chromosome and first and last marker in each linkage group are given in Table 1. The average number of analyzed markers per chromosome was 6.8. Details about the distribution of markers are given in Figure 1. Markers were chosen from previously published maps (Bishop et al., 1994; Barendse et al., 1997) and from the web site of the Meat Animal Research Center (<http://sol.marc.usda.gov/>). Marker maps were

Figure 1. Distribution of utilized markers over chromosomes in the QTL analysis. The vertical lines represent the length of the linkage group on each chromosome using the Haldane mapping function. The horizontal bars represent relative location of utilized markers on each chromosome. BTA = *Bos taurus* autosome.

established using the CRI-MAP program, version 2.4 (Green et al., 1990) and the Haldane map function.

Phenotypic Data

Daughter group averages based on records adjusted for systematic environmental effects were obtained from the national genetic evaluation. These so-called daughter yield deviations (**DYD**) were used as traits in the analyses, and they were each based on a minimum of 165 daughters per bull. The records on clinical mastitis were based on veterinary records and culling reports obtained from the milk-recording scheme. Clinical mastitis was defined as a binary trait and was scored with a 0 to 1 variable. The trait SCC was defined as the lactation mean of log-10 transformed SCC values (in 10,000/mL) obtained from the milk-recording scheme. Veterinary treatments for diseases other than mastitis and fertility problems, mainly paresis, ketosis, and hoof and leg lesions (Swedish Dairy Association, 2002), were pooled and treated as one separate trait (OD). All analyzed traits were based on records from first-lactation cows (10 d before first calving to 150 d after first calving). The heritabilities used in the analyses were derived from the genetic evaluation in Sweden. The heritability for clinical mastitis was 0.02, for SCC was 0.08, and for OD was 0.02.

Statistical Methods

Statistical methods such as least squares or maximum likelihood are used in QTL mapping to determine whether a marker or a marker bracket is associated with variation in the studied trait. Least squares methods are relatively simple to apply and computationally less demanding compared with maximum likelihood methods, thus allowing for the use of permutation tests for calculation of significance thresholds. The method we used for the QTL analyses was least squares interval mapping as described by Vilkkki et al. (1997), where the following regression model was applied for analyses at 1-cM intervals:

$$Y_{ijk} = \mu + gs_i + b_i X_{ijk} + e_{ijk}$$

where Y_{ijk} is the DYD of son k , of grandsire i , with marker genotype j ; μ is the overall mean; gs_i is the effect of grandsire i ; b_i is the regression coefficient within grandsire i ; X_{ijk} is the probability of QTL allele one being transmitted from grandsire i , given the pair of informative flanking markers j of son k ; and e_{ijk} is the residual effect. The DYD were weighted for number of effective daughters and heritability of the trait analyzed.

Initially, the chromosomes were analyzed individually to identify candidate regions for QTL. The analyses were

performed both across and within families. To increase the power of the analysis, putative ($P_{\text{chromosome}} < 0.10$) QTL found in the across-family analysis were included as cofactors in the further analyses (de Koning et al., 2001). The effects of the chosen cofactors were re-estimated jointly with multiple linear regression. The phenotypic data were adjusted for the effects of cofactors, and then the linkage groups were re-analyzed by interval mapping. The analyses were repeated until no new QTL were found. Chromosome significance levels were set by permutation tests (10,000 rounds) within and across families (Churchill and Doerge, 1994). Genomewide significance thresholds were calculated from chromosomewise thresholds by using the Bonferroni correction for testing across multiple chromosomes, $P_{\text{genome}} = 1 - (1 - P_{\text{chromosome}})^c$, where c is the total number of cattle autosomes ($c = 29$).

RESULTS

The estimated genetic length for each chromosome (*Bos taurus* autosome = **BTA**) is shown in Figure 1. The marker maps that were used sometimes deviated in length compared with other published maps (Bishop et al., 1994; Barendse et al., 1997) and the linkage map on the web site of Meat Animal Research Center (<http://sol.marc.usda.gov/>), but the order of the markers did not differ. Number of informative (sire heterozygous) markers within each family, averaged across families, varied between 2.5 and 7.3 (Table 1). Heterozygosity measured as the percentage of informative markers per grandsire ranged from 57 to 71% among the 10 sires.

The QTL effects detected in the across-family analysis are given in Table 2, presented by chromosome and trait. We detected a total of 11 suggestive ($P_{\text{chromosome}} < 0.05$) QTL, 3 of which showed a genomewide significance ($P_{\text{genome}} < 0.05$). The number of families segregating ($P_{\text{chromosome}} < 0.10$) for each QTL (Table 2) varied between 2 and 5 of 10 families.

On BTA9 and 11, we found QTL for all 3 traits (Figure 2). On BTA9, the detected QTL were located toward the distal end of the chromosome, whereas on BTA11 the QTL were located at the proximal end. Two families segregated for both mastitis and SCC at approximately the same region of BTA9. Altogether, QTL affecting clinical mastitis were found on 3 chromosomes (BTA9, 11, and 25). On BTA23, a QTL for SCC was found in the across-family analysis, and, in addition, there were individual families segregating for both clinical mastitis and OD in the within-family analysis. On BTA25, we detected QTL for clinical mastitis and OD, and in the within-family analysis, one family segregated for SCC. In total, 4 QTL were found to have an effect on SCC

Table 2. Quantitative trait loci for health traits analyzed across 10 grandsire families of Swedish dairy cattle.¹ Results are given per chromosome.²

BTA ³	Trait	Marker or marker bracket	<i>P</i>		Family ⁴
			Chromosome	Genome	
5	SCC	BM6026	*	NS	2, 7, 9
9	Clinical mastitis	TGLA73	**	†	2, 6, 7, 9
	SCC	CSSM56	**	NS	6, 7, 10
	Other diseases	UWCA9-TGLA73	**	†	1, 3, 5
11	Clinical mastitis	INRA177	*	NS	5, 9
	SCC	BMS7169	***	**	2, 7, 9, 10
	Other diseases	INRA177	***	*	2, 3, 4, 8
15	Other diseases	RM4	**	NS	1, 2, 4, 5, 10
23	SCC	BM1443	*	NS	4, 10
25	Clinical mastitis	ILSTS102-RM404	*	NS	2, 3, 6
	Other diseases	ILSTS102	***	*	2, 3, 6, 10

¹Nine families of the Swedish Ayrshire breed and one of the Swedish Holstein family.

²Only results with a significance of $P < 0.05$ are shown.

³BTA = *Bos taurus* autosome.

⁴Code number of segregating ($P < 0.10$) families.

† $P < 0.10$.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

(BTA5, 9, 11, and 23) and on OD (BTA9, 11, 15, and 25), respectively.

DISCUSSION

Significant QTL were detected for all 3 traits in the study. One reason for this is the relatively high reliability of the phenotypic data caused by a large number of observations per sire (minimum of 165; median of 309 daughters per sire). The results that are presented in Table 2 are QTL found in the across-family analysis with a chromosomewise significance of $P < 0.05$. Additional putative QTL that did not reach the chromosomewise significance threshold in the across-family analysis were detected in individual families on several chromosomes (results not shown). In general, an effect in a single family is not sufficient to make the QTL significant in the across-family analysis. However, it is not unlikely that only a small proportion of the grandsires in the population segregate for the QTL. Thus, results that only show within-family significance should not be neglected, even if more families need to be studied to determine whether these QTL are genuine.

On BTA9, we found QTL for all 3 traits analyzed. In 2 families, QTL were detected in the same chromosomal region for clinical mastitis and SCC, indicating that the same QTL could have an effect on both traits. In the across-family analysis, the peak positions of the QTL for clinical mastitis and SCC were located about 20 cM apart. Given the low mapping resolution of this study, it is not possible to determine whether the effects were

caused by the same QTL or not. Boichard et al. (2003) detected a QTL with an effect on SCC within the same area of the chromosome. The QTL for OD found in this study was located in the same region on BTA9 as the QTL for SCC and clinical mastitis; however, this QTL resulted mainly from effects in other families as opposed to those contributing to the udder health QTL. Thus, it is not evident whether there was more than one QTL for health traits in this region. To our knowledge, no QTL for OD have been described on BTA9 previously.

On BTA11, we found strong evidence for QTL affecting SCC (genomewise significance) and clinical mastitis. One family segregated for both traits in similar positions, although not in the same marker interval. The overall best positions for the 2 QTL were located 16 cM apart. Quantitative trait loci affecting SCC have previously been mapped to BTA11 (Schulman et al., 2002). A genomewise significant QTL affecting OD was also mapped to BTA11 close to the QTL for clinical mastitis. A medium high positive genetic correlation (0.53) between clinical mastitis and other diseases (Lund et al., 1994) indicates that cows that are susceptible to mastitis also tend to be more predisposed to other health problems. Also on BTA25, QTL affecting both OD and clinical mastitis were found. Three families segregated for both traits in similar positions, thus indicating a single QTL with a pleiotropic effect on the 2 correlated traits. The QTL for OD and clinical mastitis on BTA25 has not been described previously.

On BTA5, a suggestive QTL for SCC was found. Heyen et al. (1999) also detected a QTL for SCC on BTA5 but

Figure 2. Profile of test statistic from an across-family QTL analysis of different map positions on chromosomes 9 (a) and 11 (b). The bold line represents clinical mastitis, open squares represent SCC, and the thin line represents other diseases. Horizontal lines indicate approximate thresholds for chromosomewise and genomewide significance levels for the traits. Positions of the markers are indicated by triangles on the horizontal axis.

at the opposite end of the chromosome. However, there were no indications of a QTL affecting clinical mastitis on this chromosome, despite the genetic correlation between the traits. The QTL for SCC on BTA23 is supported by the findings of a number of groups (Ashwell et al., 1998; Elo et al., 1999; Heyen et al., 1999). In the within-family analysis, one family segregated for a clinical mastitis QTL in the same position as the QTL for SCC. On BTA15, Boichard et al. (2003) detected a genomewide significant QTL for SCC, a QTL that was not confirmed in our across-family analysis, although we detected QTL in individual families for both SCC and clinical mastitis. In addition, on BTA15, 5 families segregated for QTL affecting OD, and this QTL was supported by Schulman et al. (2002).

Our study only covered a part of the genome, making it impossible to reproduce some of the previously reported QTL on other chromosomes. The QTL for clinical mastitis that were reported on 5 chromosomes (BTA3, 4, 6, 14, and 27) in Norwegian dairy cattle (Klungland et al., 2001) were not confirmed in the across-family analysis of this study. However, there were indications of QTL segregating in individual families on BTA3, 4, and 14. (BTA27 was not included in our analysis.) Although we found no indications of a QTL for clinical mastitis on BTA6, one family showed segregation for a QTL affecting SCC on this chromosome. In a study of Finnish Ayrshire cattle, Schulman et al. (2002) found QTL for clinical mastitis on BTA14 and 18. One family in the present study showed segregation for a QTL for clinical mastitis on BTA18; the same family also segregated for a QTL affecting SCC on BTA18. In total, 3 families showed effects of a QTL for SCC on BTA18, but the effects were not significant in the across-family analysis. Several previous studies have reported QTL for SCC on BTA18 (Ashwell et al., 1997; Schrooten et al., 2000; Schulman et al., 2002; Bennewitz et al., 2003; Kuhn et al., 2003).

In the study by Klungland et al. (2001), no overlaps were found between QTL locations for SCC and clinical mastitis in the Norwegian dairy cattle population. Their results indicate that clinical mastitis and SCC monitor different aspects of udder health. Estimates of the genetic correlation between SCC and clinical mastitis differ substantially between studies, but the correlations are generally moderately high to high (Emanuelson, 1997). In our study, many of the QTL found for SCC and clinical mastitis were located within the same chromosomal region and some QTL even in similar positions. Our results support the hypothesis that loci with influence on SCC may also contribute to the genetic variance in mastitis resistance. However, in addition, there seem to be QTL specific for clinical mastitis or SCC, which is why it is important to consider both traits in a selection program. Coinciding QTL locations of all 3 traits in similar chromosomal regions suggest either a QTL with a pleiotropic effect on correlated traits or several QTL with an effect on different traits clustered in the same chromosomal region.

Other traits that are of importance to udder health are udder conformation and milking speed, which both are correlated with SCC and clinical mastitis. Published estimates of genetic correlations are, however, low to moderate (Lund et al., 1994; Rupp and Boichard, 1999). Some studies have found QTL for udder conformation and milking speed and previously detected QTL on chromosomes where we detected QTL for SCC and/or clinical mastitis; these are listed in Table 3. On all the chromosomes where we found QTL for udder health, there is at least one QTL reported for an udder conformation trait.

Table 3. Results from studies on detection of QTL for traits related to udder health given by chromosome.

BTA ¹	Trait	Study	Marker or marker bracket	Breed
5	Udder depth	Schrooten et al. (2002)	IGF1-BM315	Holstein Friesian
	Rear udder height	Schrooten et al. (2002)	AGLA254-IGF1	Holstein Friesian
	Milking speed	Boichard et al. (2003)	CSSM022	Three French breeds ²
9	Rear udder attachment	Boichard et al. (2003)	RM500	Three French breeds ²
	Udder depth	Boichard et al. (2003)	INRA144	Three French breeds ²
	Teat placement front	Boichard et al. (2003)	UWCA9	Three French breeds ²
11	Rear udder attachment	Boichard et al. (2003)	UWCA9	Three French breeds ²
	Rear udder height	Ashwell et al. (1998a)	BM304	United States Holstein
	Udder depth	Ashwell et al. (1998b)	BM1258	United States Holstein
23	Fore udder attachment	Schrooten et al. (2002)	RM033	Holstein Friesian
	Milking speed	Schrooten et al. (2002)	BM1258-GBCYP21	Holstein Friesian
	Milking speed	Elo et al. (1999)	BoLA DRBP1	Finnish Ayrshire
25	Fore udder attachment	Schrooten et al. (2002)	BP28-BMS1353	Holstein Friesian

¹BTA = *Bos taurus* autosome.

²French Holstein (9 families), Normande (3 families), and Montbéliarde (2 families).

To confirm the results obtained on BTA9 and 11, 2 chromosome regions were genotyped for 2 microsatellites each in 18 additional families (data not shown). The families were smaller than in the main study, comprising 15 to 34 sons. The markers were BMS2819 and BMS1967 on BTA9 and INRA177 and BM6445 on BTA11. Analyses were made by the same method as in the main study. Despite the small families, we were able to confirm the QTL for clinical mastitis on BTA9 in the across-family analysis; however, only one family segregated ($P < 0.05$) for the SCC QTL. On BTA11, we were not able to confirm our previous results from the across-family analysis, but the clinical mastitis QTL segregated in two families ($P < 0.05$), and the QTL for SCC segregated in one family. Because of the relatively small family sizes in the Swedish dairy cattle population, the power of the analysis using a granddaughter design is limited. To increase the power of the analysis and also to find out whether our results are influenced by pleiotropic effects or genetic linkage, a multitrait analysis could be performed because the analyzed traits are correlated. To improve the mapping resolution and get more precise locations of the QTL detected in this study, we need to use a denser genetic map and other methods of analysis such as linkage disequilibrium mapping.

In addition to the 3 disease traits that we have focused on in this paper, we have also performed a preliminary QTL analysis on milk production traits on the same family material. The unfavorable genetic correlation between mastitis frequency and milk production might have contributed to some of the detected QTL for clinical mastitis. It is possible that a QTL with effect on factors that control milk yield could have an indirect effect on clinical mastitis frequency and show up as a QTL for mastitis. In our study, we only found one QTL with an effect on milk yield that overlapped a QTL for clinical mastitis. The QTL were found on BTA9 in the same

marker interval. A few other studies have reported QTL for milk yield on BTA9 (Georges et al., 1995; Wiener et al., 2000; Plante et al., 2001). This illustrates that caution should be taken before drawing any conclusions about detected QTL. It is important to find out whether a QTL for milk production has negative effects on udder health traits before applying the results in breeding programs by use of marker information.

CONCLUSIONS

In this study, previously unknown QTL for clinical mastitis and OD were unveiled and previously detected QTL were confirmed. We found QTL for all 3 traits on chromosomes 9 and 11. In total, 8 suggestive QTL and 3 significant QTL were detected. Further research is needed to get a more precise location of the QTL and to reveal the genetic background of the QTL effects.

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